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Improving outcomes of patients with Alzheimer's disease

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Chapter 4

Main Findings and General Discussion

In the previous chapters, each study was discussed in detail. In this chapter, the main findings of the studies will be discussed in a broader perspective. We will conclude every section of this chapter with recommendations for future research and for clinical practice.

Since Alzheimer's disease (AD) is one of the most disabling and burdensome health conditions worldwide¹, it is crucial to improve the outcomes for AD patients. In order to improve the outcomes for AD patients, this thesis focused on the long-term course of AD in patients treated in a 'real-life' setting and their nutritional status.

LONG-TERM COURSE OF ALZHEIMER'S DISEASE IN PATIENTS TREATED IN A 'REAL-LIFE' SETTING

Long-term course of Alzheimer's disease

The long-term disease course of 576 AD patients from the Frisian Alzheimer's Disease Cohort, who were treated with pharmacological and non-pharmacological interventions provided in a 'real-life' setting, was described in chapter 2.1. The 'real-life' setting avoided the limitations of most AD clinical trials, thereby increasing the external validity of the results. Our results showed that cognition and behaviour of the AD patients deteriorated accompanied with an increase in care-dependency during 3.5 years of follow-up (chapter 2.1). Nevertheless, compared to the disease progression observed in the period before cholinesterase inhibitors (ChEIs) were available, the pharmacological and non-pharmacological interventions appeared to slow cognitive decline, which is in line with results from other long-term, 'real-life' cohorts²⁻⁴. This emphasizes that the combination of pharmacological and non-pharmacological interventions seems to have favorable effects on the long-term cognitive outcome of AD patients.

It was not possible to be conclusive as to whether the pharmacological and non-pharmacological interventions provided at our memory clinic had a favourable effect on other patient-relevant outcomes such as behavioural and psychological symptoms (BPS), (Instrumental) Activities of Daily Living (I)ADL, nursing home admission and mortality. Unfortunately, these important outcomes have not been studied well to date⁵. Nevertheless, there is evidence, based on long-term 'real-life' studies, that ChEIs show benefit on nursing home admission²⁻⁴. Nursing home admission is an important outcome from a patient as well as from an economic perspective. At this moment, dementia is, with 5% of the total health care costs, the most expensive health care condition in the Netherlands⁶. The majority of these costs represent costs for institutionalized patients^{6,7}. Furthermore, most elderly people prefer to live in their own home as long as possible⁸. It may be preferable for dementia patients to remain in their homes, not only for economic reasons, but also because they remain able to maintain the integrity of their social network and enjoy a better quality of life^{8,9}. Therefore, it is important to focus on possibilities that enable patients with dementia to remain in their own home as long as possible. In this context, it is important to note that we showed that BPS is associated with nursing home admission (chapter 2.1). This finding is in line with other studies^{9,10}. In addition, it has

been shown that weight loss in AD patients is associated with a higher rate of institutionalization¹¹, which underlines the importance of research to the nutritional status of AD patients, which will be discussed in the next paragraph. Firstly, we will discuss the relation between the initial response to ChEI treatment and the subsequent course of AD.

Response to cholinesterase inhibitors in Alzheimer patients

In order to improve outcomes of AD patients, evidence based treatment recommendations are relevant as they may help clinicians, patients and their caregivers to make informed decisions. There is limited evidence that underpins the recommendations with regard to what clinicians should do in case of absence of a treatment response to ChEIs¹². In order to support the decision to stop or to continue treatment in case of absence of a response, we investigated the relation between the initial response to ChEI treatment and the subsequent long-term course of AD by comparing the long-term course of cognition between initial cognitive non-responders and responders (chapter 2.2). Our results showed that non-responders had a slower rate of cognitive decline during the subsequent 3 years than cognitive responders (chapter 2.2). The rate of cognitive decline in non-responders was also slower compared to the rate of decline in historical cohorts with untreated patients (chapter 2.2). These results suggest that, despite absence of an initial cognitive response to treatment with a ChEI, treatment can be beneficial in reducing the rate of cognitive decline during subsequent long-term course in AD patients. Therefore, we think that it is not appropriate to discontinue ChEI treatment solely based on the absence of an initial cognitive response.

To date, various studies have investigated factors that predict treatment response¹³⁻²². There are however just a few studies that investigated the clinical relevance of the presence or absence of a treatment response. Although, recently, the relationship between the 6-month response to ChEI treatment and lifespan of AD patients was investigated by Wattmo et al.²³. Like in our study, a positive cognitive response was defined as the same or a higher MMSE score compared to baseline after 6 month of treatment, absence of a response as a lower MMSE score. Wattmo et al. showed that AD patients with a positive cognitive response based on the MMSE had a longer lifespan of 0.5 years. In addition, AD patients with a positive response regarding functional capacity and global performance also had their lifespan prolonged with a few months²³. However, this was not observed for patients with a positive cognitive response based on the ADAS-cog score.

When interpreting our results, it must be taken into consideration that the change in MMSE score was the only measure available to determine treatment response. Although our definition was based on an outcome measure most often used in clinical practice and as described in the Dutch guideline regarding the management of AD²⁴, it can not be assumed that this definition of treatment response correlates with what is considered a relevant outcome by patients and their caregivers. Unfortunately, no consensus exists regarding the definition of treatment response. Moreover, in the decision to stop or to continue treatment, other factors may play a role, such as adverse events of treatment with ChEIs and personal opinions and values of patients and their caregivers²⁴.

Recommendations for future research and for clinical practice

Because our results show that the combination of pharmacological and non-pharmacological interventions seem to have favorable effect on the cognitive outcome of AD patients (chapter 2.1), we feel that treatment with these interventions should be encouraged in clinical practice. As long there is no consensus regarding the definition of an initial response to treatment with a ChEI and the clinical relevance of the presence or absence of an initial response, absence of an initial cognitive response should not be a reason to discontinue ChEI treatment (chapter 2.2).

Since it was not possible to be conclusive as to whether the pharmacological and non-pharmacological interventions had a favourable effect on other patient-relevant outcomes like BPS, (I)ADL, nursing home admission and mortality (chapter 2.1) and because these important outcomes are not well studied to date⁵, we feel that more ‘real-life’ studies are needed in order to establish whether these interventions have a positive effect on these patient-relevant outcomes. In particular, we recommend investigating the effect of pharmacological and non-pharmacological interventions, including nutritional interventions, on nursing home admission, since nursing home admission is an important outcome from a patient as well as from a societal and economic perspective⁶⁻⁹. Following this train of thought, we also recommend investigating more treatment options for BPS in AD, since we and others have shown that BPS is associated with nursing home admission (chapter 2.1).

In order to support the decision to stop or to continue treatment in case of absence of an initial response, more research is needed. Research should focus on the one hand on defining what can be regarded as a patient-relevant treatment response; i.e. is it possible to define a patient-relevant treatment response on a combination of changes in various rating scales? Or, could a simple perception of benefit by the patient or caregiver be an indicator of a patient-relevant treatment response and hence be helpful in the decision to continue ChEI treatment or not. On the other hand, additional studies are warranted to confirm our findings. Regardless of the relation between the initial cognitive response and the subsequent long-term course of cognition, the relation of the initial response with other outcomes (i.e. BPS, (I)ADL, nursing home admission, mortality) need to be investigated.

The disease course in our, but also in other studies, was described by various rating scales for which a definition of a worthwhile clinical response is lacking. We recommend to develop and use scales that can describe the course of AD for all patient relevant domains and provide clinically significant changes. Recently, such a scale was developed: the Relevant Outcome Scale for Alzheimer’s Disease (ROSA)²⁵, which appears to be a promising tool for the future as it could be used as a relevant outcome measure in intervention studies in AD patients. In addition, the ROSA may possibly be helpful in defining a patient-relevant (initial) treatment response. Currently, the ROSA is available in English, German and French. We recommend to translate and validate the ROSA in more languages like Dutch and Frisian, which improves the possibility to compare outcomes of AD studies from different countries.

Moreover, we recommend collecting data regarding the course of AD in well established

registries (for example the NoNe-GON database, i.e. a database including patients with dementia diagnosed in hospitals in the north of the Netherlands) using appropriate and validated scales (for example the ROSA). This offers the opportunity to use 'benchmarking' in order to improve the outcomes for AD patients. With benchmarking, the clinical approaches of institutions with superior clinical outcomes could be identified and used for the improvement of the quality of care and outcomes of other institutions²⁶.

ALZHEIMER'S DISEASE AND NUTRITIONAL STATUS

Prevalence of weight loss and undernutrition in community-dwelling Alzheimer patients

We showed that one in seven community-dwelling elderly with newly diagnosed AD was at risk of undernutrition according to the Mini Nutritional Assessment (MNA) (chapter 3.1). The prevalence of undernutrition was 0% (chapter 3.1). We were surprised about these results, because these rates are considerably lower than reported in other studies, with prevalences of risk of undernutrition (evaluated with the MNA) ranging from 26% to 80%²⁷⁻³⁴. The number of undernourished community-dwelling AD patients (according to the MNA) varies from 0% to 9%^{28,32,34}. The number of community-dwelling AD patients with weight loss, a characteristic of (risk of) undernutrition³⁵, varies between 20% and 45%³⁶⁻⁴¹. Though, a recent study showed that community-dwelling AD patients did not lose weight during four years of follow-up⁴². This wide variation in the number of community-dwelling AD patients with weight loss and (risk of) undernutrition could be explained as follows:

The highest prevalences of weight loss and (risk of) undernutrition were reported in studies from the pre-ChEI-era^{37,40,41}. Recent studies showed a decreased risk of weight loss in AD patients treated with a ChEI compared to untreated patients^{38,39,43,44}. In these studies, ChEIs appeared to protect against weight loss. In addition, it could be that weight loss and undernutrition in AD patients are currently less frequently observed due to the increased quality of care of home-dwelling AD patients. In the past decade, it is not just the pharmacological treatment that has changed the management of AD. Drugs are given in addition to multiple non-pharmacological interventions, including for instance dietary advices and provision of meals at home services^{45,46}. Gu et al. showed that the Body Mass Index (BMI) of AD patients declined up to the clinical onset of AD. After clinical onset however, there was no decrease but increase of the BMI, possibly because care was arranged after the diagnosis of AD⁴⁷. This finding is in accordance with results from our cohort; contrary to what we expected, AD patients from our cohort did not lose but gained weight during 3.5 years of follow up (chapter 3.2).

Causes and mechanisms of weight loss and undernutrition in community-dwelling Alzheimer patients

In chapter 3.2 and 3.3, we focused on causes and mechanisms of weight loss in AD patients. In chapter 3.2, we explored the role of atrophy of the medial temporal lobe in weight loss in AD patients.

We found no evidence that medial temporal lobe atrophy (MTA) is associated with weight loss in AD patients (chapter 3.2). Since we only investigated the relation between MTA and body weight, it can not be ruled out that pathology of other brain regions or other forms of brain pathology are associated with the trajectory of body weight in AD patients. Moreover, MTA was measured cross-sectionally, instead of longitudinally. Therefore, it was not possible to investigate whether e.g. percent change in MTA over time predicts weight change, nor to elucidate whether weight loss causes disease progression by aggravating MTA. If the latter is true, weight gain, for example by providing nutritional interventions, might prevent or slow MTA and possibly disease progression.

In chapter 3.3, the role of ChEIs as a potentially contributing factor in weight loss was examined. We showed that long-term treatment with galantamine had no negative effect on weight of AD patients (chapter 3.3). Although AD patients from our cohort gained weight during 3.5 years of follow up, body weight decreased during the first 6 months of treatment (chapter 3.2). This initial weight loss might be explained by the fact that (gastrointestinal) side effects of ChEIs seem to occur mainly in the beginning of treatment and are transient in nature⁴⁸. This is supported by the finding that the risk of weight loss was decreased in patients taking ChEIs for more than 3 months compared to those who had just begun to use a ChEI³⁸. Because the gastrointestinal side effects of ChEIs seem to occur mainly in the beginning of treatment and are transient in nature⁴⁸ and since we showed that long-term treatment with galantamine had no negative effect on weight of AD patients (chapter 3.3), weight loss in AD patient should in general not be a reason to stop ChEI treatment.

Effect of nutritional interventions in community-dwelling Alzheimer patients

Given the prevalence and possible adverse outcomes of weight loss and (risk of) undernutrition, it is important to know what the best approach is to community-dwelling AD patients with a risk of developing a poor nutritional status. Therefore, we conducted a systematic review of the effect of nutritional interventions in community-dwelling AD patients with (risk of) undernutrition (chapter 3.4). Despite our comprehensive literature search, only one study was judged relevant for the purpose of our review. In this study, Lauque et al. showed that an oral nutritional supplement (ONS) significantly improved nutritional outcomes (i.e. body weight, MNA, energy intake, protein intake, fat-free mass) in community-dwelling AD patients at risk of undernutrition, as evaluated with the MNA⁴⁹. However, no effect was found on clinical and biochemical outcomes⁴⁹. In addition, the risk of bias in the study of Lauque et al. was judged to be high. Due to the lack of evidence, it is not possible to state what the best approach is to community-dwelling AD patients with (risk of) undernutrition.

The lack of evidence may mean that undernutrition in community-dwelling AD patients is not so important as postulated. This is supported by the fact that one of the retrieved trials in our systematic review was terminated because of difficulties in the recruitment of AD patients meeting the inclusion criteria, including undernutrition (chapter 3.4). Moreover, it is supported by the low number of undernourished community-dwelling AD patients (chapter 3.1,^{32,34,39}).

Recommendations for future research and for clinical practice

Eventhough, frank undernutrition may be a non-issue in community-dwelling AD patients, we showed that one in seven community-dwelling elderly with newly diagnosed AD was at risk of undernutrition (chapter 3.1) and other studies reported even higher rates²⁷⁻³⁴. Given the suggested adverse outcomes of weight loss and (risk of) undernutrition, it is important to expand research to the nutritional status of community-dwelling AD patients.

Little is known about the trajectory of weight before a diagnosis of AD is made. Weight loss may be a preclinical feature of AD^{47,50}. Perhaps, weight loss in patients from our cohort occurred before the diagnosis AD was made. To support this, more prospective cohort studies are needed, starting in older subjects without AD.

In addition, research should focus on the proposed causes and mechanisms of weight loss and undernutrition in AD. For example, the relation between other brain regions or other forms of brain pathology with the trajectory of weight should be investigated. In this, we recommend to measure both the nutritional status and brain pathology longitudinally in order to make causal inferences about the relation between weight, disease progression and brain pathology.

In the absence of evidence, we will give expert based practical recommendations on how to approach the nutritional status of community-dwelling AD patients. In 2007, Belmin et al. provided a practical guideline for the diagnosis, management and prevention of weight loss in AD⁵¹. This guideline is based on a 23-member expert panel drawn from French geriatricians⁵¹. We support these practical recommendations, which are summarized in figure 1 and described here:

We do believe that the nutritional status should be part of the work-up of all AD patients. The recommendation in the guideline of Belmin et al. is to assess the nutritional status for every AD patient at the time of diagnosis and/or the start of treatment. Nutritional assessment of a newly diagnosed AD patient comprises at least measurement of weight and performing the MNA. It is important to note that, to account for the cognitive problems associated with AD, the MNA must be obtained with the help of the family and/or caregiver⁵¹. The recommendation with regard to nutritional follow-up of AD patients comprises at least monthly weighing⁵¹.

If weight loss of 5% or more has occurred in 3 to 6 months or if the MNA classifies a patient as undernourished, a nutritional intervention should be started⁵¹. The nutritional interventions described by Belmin et al. are 1) searching for reversible medical or socioenvironmental causes, 2) increase calorie and protein intake and 3) daily physical activity⁵¹. Like Belmin et al., in our opinion, treatment of weight loss and (risk of) undernutrition in community-dwelling AD patients should be multifactorial and encompass treatment of the underlying proposed causes and risk factors of weight loss and undernutrition as well as improvement of the nutritional status by increasing energy and protein intake in combination with daily physical activity.

Interventions targeting the underlying proposed causes and risk factors of weight loss and undernutrition
As shown in figure 1 of the general introduction (chapter 1), it could be that general factors such as

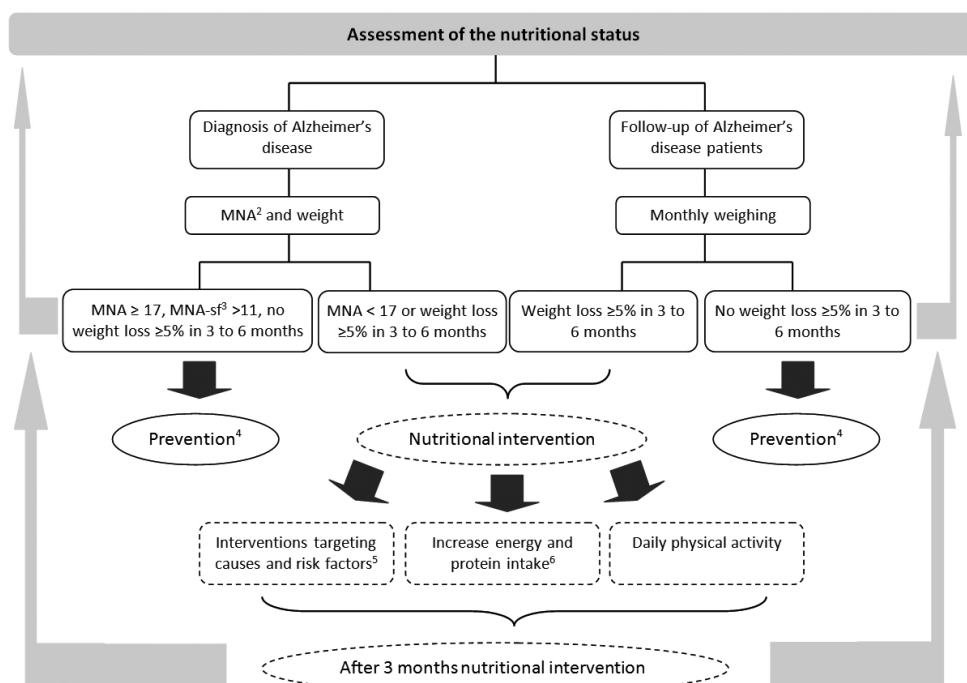


Figure 1: Approach to the nutritional status of community-dwelling patients with Alzheimer's disease¹

¹ Figure 1 is based on expert based recommendations, partly derived from the guideline of Belmin et al. 2007 (51); ² Mini Nutritional Assessment; ³ MNA-short form; ⁴ By a varied, balanced diet and daily physical activity; ⁵ See figure 1 Chapter 1; ⁶ By dietary fortification, dietary counselling and oral nutritional supplements. I.e.: energy goals: at least 400 kcal extra per day, with a minimum of 1500 kcal/day, protein goals: 1.2 g/kg body weight/day.

side effects of medication or social factors as loneliness or poverty contribute to weight loss in AD patients. Therefore, these factors need to be addressed. In chapter 3.1, we showed that the degree of impairment in daily functioning is independently related to nutritional status. In addition, we showed that community-dwelling AD patients without an informal caregiver or partner had a lower average weight compared to patients with an informal caregiver or partner (chapter 3.3). Therefore, if AD patients are developing a poor nutritional status, it is important to establish whether care is sufficient and if necessary that appropriate care is arranged, for example starting meals at home services or supervision of meal intake.

Increase energy and protein intake

In agreement with Belmin et al., we recommend dietary counselling, dietary fortification and ONS to increase calory and protein intake. Despite the limited evidence, the only study that was relevant for the purpose of our recently published systematic review showed that ONS significantly improved nutritional outcomes in community-dwelling AD patients at risk of undernutrition⁴⁹. The ONS used contained between 300 and 500 kcal in addition to the patients' spontaneous food intake and

was enriched with proteins, vitamins and minerals. It was given for three months. With regard to energy intake, we recommend that at least 400 kcal extra per day is added with a minimum of 1500 kcal/day³⁵. Protein need in older patients is suggested to be as high as 1.2 g/kg body weight/day³⁵. We recommend to continue the nutritional intervention for at least three months, because it is supposed that at least three months is needed to improve the nutritional status by a nutritional intervention³⁵. If an ONS is prescribed, it is important that there is someone who ensures that the patient is adherent to this intervention.

Daily physical activity

Daily physical activity prevents muscle wasting, stimulates appetite and so restores energy balance in AD patients⁵². In addition, when dietary fortification and/or ONS are combined with simple physical activity, for example a fifteen minute walk every day, it is more likely that the additional calories and proteins will be converted into muscle mass, which in turn will improve functioning⁵³.

Belmin et al. recommend a varied, balanced diet and daily physical activity for every AD patient to prevent weight loss and undernutrition⁵¹. In addition, they advise that health care professionals and family should follow a training course that focuses on the nutritional status of AD patients⁵¹.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

In order to improve the outcomes for AD patients, this thesis focused on the long-term course of AD in patients treated in a 'real-life' setting and their nutritional status. Based on the results of this thesis we recommend the following to improve the outcomes for AD patients:

1. Treatment with the combination of pharmacological and non-pharmacological interventions should be encouraged in clinical practice.
2. As long as there is no consensus regarding the definition of an initial response to treatment with a ChEI and the clinical relevance of the presence or absence of an initial response, absence of an initial cognitive response should not be a reason to discontinue ChEI treatment.
3. There should be a definition of what is understood by an initial response to treatment with a ChEI, for example by performing a Delphi study.
4. Weight loss in AD patients should not be a reason to stop ChEI treatment.
5. More 'real-life' studies are needed in order to establish whether pharmacological and non-pharmacological interventions have a positive effect on other patient-relevant outcomes, in particular nursing home admission and BPS.
6. We recommend to develop and use scales that can describe the course of AD for all patient relevant domains and provide clinically significant changes.
7. Data regarding the course, including the nutritional status, of AD should be collected in well established registries (for example the NoNe-GON database) using appropriate and validated scales (for example the ROSA) so that 'benchmarking' could be used to improve the outcomes

for AD patients.

- 8.** The nutritional status should be part of the work-up of all AD patients. In the absence of evidence, our expert based practical recommendations are:
 - a.** Nutritional assessment of a newly diagnosed AD patient should comprise at least weighing and performing the MNA, nutritional follow-up should comprise at least monthly weighing.
 - b.** If weight loss of 5% or more has occurred in 3 to 6 months or if the MNA classifies a patient as undernourished, a nutritional intervention should be started.
 - c.** A nutritional intervention should be multifactorial and encompass treatment of the underlying proposed causes and risk factors of weight loss and undernutrition as well as improvement of the nutritional status by increasing energy and protein intake combined with daily physical activity.
 - d.** We recommend a varied, balanced diet and daily physical activity for every AD patient to prevent weight loss and undernutrition.
- 9.** We recommend to expand research to the nutritional status of AD patients, including research to the proposed causes and mechanisms of weight loss and undernutrition and the effect of nutritional interventions in community-dwelling AD patients with a poor nutritional status.

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